REMARKS

Claim 22 has been amended to incorporate the limitations of prior claim 26, and claim 26 has been cancelled herein. Support for the amendments lies in the specification and original claims as filed. For example, support for the amendment to claim 22 lies in original claim 26, as well as at least at paragraphs [009], [014] and [079] of the publication of the application (U.S. Patent Application Publication No. US2005/0009918A1). No new matter is added by virtue of the amendments contained herein.

Claims 22, 23, and 25-28 were rejected under 35 USC 112, second paragraph as indefinite because of recitation of the phrase "penetration enhancer" and "shear-thinning polysaccharide gum" in Claim 22.

Claim 22 has been amended. It is believed the amendments render the rejection moot. Reconsideration and withdrawal of the rejection is respectfully requested.

Claims 22, 23, and 25-28 were rejected under 35 USC 102(b) as anticipated by Buyuktimkin et al. (US 6,046,244). The rejection is traversed.

The conclusion of the Office Action is that Buyuktimkin meets the limitations of the claims because the composition of Buyuktimkin is described as applied to the skin of a patient "since the purpose of Buyuktimkin is to transdermally administer prostaglandin containing composition to treat peripheral vascular disease to maintain open blood vessels." See Office Action at page 3.

In order to effectively anticipate a claim, a reference must teach each and every limitation of the claim. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). While Applicant agrees the composition described in Buyuktimkin is similar to that used in the present methods, Applicant respectfully submits the use of the composition for treatment of vasospasm is not the same as treatment of peripheral vascular disorder as described in Buyuktimkin. There is no teaching in Buyuktimkin to topically apply to a region of a subject's tissue requiring treatment of vasospasm an effective amount of a semi-solid composition.

Peripheral vascular disease, or peripheral arterial disease, is disease caused by obstruction of the peripheral arteries, and may be caused by atherosclerosis, inflammation and stenosis, embolism, or thrombosis. See "Peripheral Arterial Disease" in *Merck Manual of Medical Information—Second Home Edition Online Edition.*at www.merck.com/mmpe/sec07/ch080/ch080f. 2004-2008; and "peripheral vascular disease" in *Online Medical Dictionary* at //cancerweb.ncl.ac.uk/cgi-bin/omd?query=peripheral+vascular+disease. 1997-2007. In contrast, vasospasm refers to conditions

where blood vessels spasm, leading to vasoconstriction. See, e.g., See "Raynaud's Phenomenon" in *Merck Manual of Medical Information—Second Home Edition Online Edition.*at www.merck.com/mmpe/sec07/ch080/ch080g. 2004-2008; "Acrocyanosis" in *Merck Manual of Medical Information—Second Home Edition Online Edition.*at www.merck.com/mmpe/sec07/ch080b. 2004-2008; and "vasospasm" in *Online Medical Dictionary* at //cancerweb.ncl.ac.uk/cgi-bin/omd?query=vasospasm. 1997-2007. Thus, the disclosure of Buyuktimkin referring to treatment of peripheral vascular disease is not the same as disclosing treatment of vasospasm. Thus, Buyuktimkin does not anticipate the present claims. Reconsideration and withdrawal of the rejection is requested.

Claims 22, 23, and 25-28 were rejected under 35 USC 103(a) as unpatentable over Buyuktimkin et al. (US 6,046,244) in view of Clifford et al. (Br. Med. J. 1980 October 18; 281(6247): 1031-1034). Applicant respectfully traverses the rejection.

The Office Action summarizes the teaching of Buyuktimkin as teaching "keeping open blood vessels is treating narrowing of the blood vessels". The Office Action concludes that since Clifford discloses Prostaglandin E_1 is used to treat vasospastic disease, one skilled in the art would reasonably expect to successfully treat vasospasm or maintain open blood vessels by transdermally/topically applying the semi solid composition of Buyuktimkin to the skin of a patient. See Office Action mailed 12/03/07 at page 5, first paragraph.

Applicant respectfully submits the disclosure of Clifford would not render obvious the present claims. The teaching of Clifford relates to intravenous infusion of Prostaglandin E_1 to treat severe vasospastic disease (Raynaud's). Clifford recognizes that "(m)anagement of patients suffering from severe Raynaud's phenomenon with or without trophic skin changes remains controversial;" and, "(v)asodilators, sympathectomy, plasma exchange, and fibrinolytic enhancement are used with varying effect." See Clifford at page 1031, right column, the second paragraph of Introduction. Additionally, Clifford describes high doses of venous infusion of Prostaglandin E_1 are required for effective delivery of Prostaglandin E_1 in order to achieve a therapeutic dose reaching arterial circulation. See Clifford at page 1033, left column, the second paragraph of Discussion. Furthermore, the discussion of Clifford summarizes that results of the infusion studies support "the argument that it acts locally on vascular endothelium, which, in atherosclerosis, is depleted of prostaglandins."

The present claims relate to topical application of a semi solid composition for delivery of Prostaglandin E_1. Because treatments with a variety of therapies have been found to demonstrate only inconsistent efficacy, delivery of therapeutically effective doses of Prostaglandin E_1 has been shown to be difficult, and the pharmacological site of activity of the active agent is the endothelium of the vasculature, one would certainly not expect that topical delivery of Prostaglandin E_1, including the semi solid

composition of Buyuktimkin, would be successful for delivery of an effective amount of Prostaglandin E_1 to the endothelium of the vasculature in order to demonstrate efficacious response and treatment of vasospasm, particularly in view of the disclosure and conclusions of Clifford. Rather, Applicant contends when the teachings of Buyuktimkin is assessed in view of the disclosure of Clifford, one skilled in the art would not expect that topical delivery of a semi solid composition of Buyuktimkin would successfully deliver a therapeutically effective dose of Prostaglandin E_1 to the endothelium of the vasculature for effective treatment of vasospasm.

Furthermore, the disclosure of Clifford recognizes the differences of treatment of vascular disorders, including discriminating the treatments of vasospastic disease and peripheral vascular disease. See e.g., Clifford at page 1301, right column, the second paragraph of Introduction. Clifford also acknowledges that while Prostaglandin E_1 infusion was found an effective method for treating vasospastic disease, further studies are warranted to determine whether Prostaglandin E_1 has a role for treatment in peripheral vascular disease. See, e.g., Clifford at page 1033, right column, the second full paragraph.

In conclusion, Applicant submits in view of the teaching as a whole of the disclosures of Buyuktimkin and Clifford, the instant claims would not be obvious. Reconsideration and withdrawal of the rejection of the claims is therefore respectfully requested.

This paper is being filed timely as it is being filed with a petition and request for a one month extension of time and the associated fee. It is believed no additional fees or extensions of time are required. In the event any additional extensions of time are necessary, please consider this a petition therefor. In the event any fees or credits are due, the undersigned hereby authorizes the fees or credits to be charged to Deposit Account No. 50-1582.

Entry of the remarks made herein is respectfully requested.

Respectfully submitted,

April 3, 2008 MIRICK O'CONNELL DEMALLIE & LOUGEE, LLP

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